REMARKS

Claims 1-8 and 11-16 were pending. Claims 12, 14 and 16 are currently amended. No new matter has been added. Support for the amendments to the claims can be found throughout the specification and claims as filed and in particular paragraphs [0135], [0136], [0160] and [0190] and the Examples. In view of the arguments provided herein, Applicants respectfully request reconsideration of claims 1-8 and 11-16.

Rejections under 35 USC § 112, second paragraph

The Examiner has rejected claims 1-8 and 11-16 under 35 U.S.C. § 112, second paragraph as being indefinite allegedly for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Specifically the Examiner has alleged that the claims are incomplete as an essential step is omitted. The Examiner further states that the wherein clause in step c merely sets forth a property f the method, but does not indicate how the method accomplishes the objective of characterization, prognosis, etc by merely performing the steps of obtaining a sample and determining methylation.

Applicants respectfully disagree and traverse the rejections over claims 1-8 and 11-16 under 35 U.S.C. § 112, second paragraph.

Applicant contends that the rejections with respect to claims 1-8 and 11-16 are moot in view of Applicant's amendments to the claims.

Specifically, claim 1 has been amended include a step in which the methylation state of a sample taken from a subject having or at risk a cell proliferative disorder of the breast with the methylation state of a subject who is not having a cell proliferative disorder of the breast or at such risk. Accordingly, Applicant respectfully requests withdrawal of the Examiner's rejections under 35 U.S.C. § 112.

The Examiner further contends that there is no "wherein" clause in claim 1. Applicants respectfully request that the Examiner reread the claim as the wherein clause is located in the in the last paragraph, claim 1 specifically states:

> "determining, based on the methylation [~~status~~] state characteristics of the cell proliferative disorder of the subject breast tissue, thereby providing one or more of a prognosis of said subject disease free survival or metastases of said subject; and/or probability of response of said subject to one or more treatment regimens **wherein** an increased methylation [~~status~~] state in the sample as compared with methylation [~~status~~] state in a control sample from a subject not having or at risk of having a cell proliferative disorder of the breast tissue, provides characterization of the cell proliferative disorder?" (emphasis added)

Applicant respectfully requests withdrawal of the Examiner's rejections under 35 U.S.C. § 112.

B) The Examiner states that claim 1 recites 'DNA from breast cells or tissue; breast tissue or breast cell sample' and therefore the metes and bounds of the claims are unclear. Applicants have amended claim 1 to correct a typographical error and to recite 'DNA from a biological fluid containing DNA from breast cells or tissue; breast tissue; or breast cell sample.' Applicant contends that this rejection is moot in view of Applicant's amendments to the claims and requests withdrawal of the Examiner's rejections under 35 U.S.C. § 112.

Rejections under 35 USC § 112, first paragraph

The Examiner has rejected claims 1-8 and 11-16 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner alleges that the claims have been amended to include a comparison step with a subject not having or at risk of having a cell proliferative disorder of the breast tissue and that the paragraphs pointed out by the Applicant, [0051]-[0069] and the specification generally, do not appear to teach such a comparison step.

Applicants respectfully disagree. Claim 1 has been amended to recite the comparison step with a subject not having or at risk of having a cell proliferative disorder of the breast tissue as described by the Examiner but Applicants contend that the specification contains more than adequate support for written description. Support for this amendment can be found in paragraph [0135], page 13 of the present application which recites:

> 'In the context of the present invention the term "methylation state" is taken to mean the degree of methylation present in a nucleic acid of interest, this may be expressed in absolute or relative terms i.e. as a percentage or other numerical value or **by comparison to another tissue** and therein described as hypermethylated, hypomethylated or as having significantly similar or identical methylation status.' (emphasis added)

One skilled in the art would understand that such comparison to another tissue would include comparison to a subject not having or at risk of having a cell proliferative disorder of the breast tissue

Applicant respectfully requests withdrawal of the Examiner's rejections under 35 U.S.C. § 112.

Rejections under 35 USC § 112, first paragraph

The Examiner has rejected claims 1-8 and 11-16 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

Specifically, the examiner alleges that the present invention lacks enablement for a broad range of treatments which differ in structure and mechanism of action; a broad genus of

disorders; for the methylation status of one or more CpG dinucleotides over a large stretch of DNA; how the results of determining methylation status are used to characterize, prognose, determine disease free survival or responsiveness to therapy for a cell proliferative disorder of the breast or working examples of such; and lastly the Examiners states that the current state of the art for using PITX2 methylation as a predictor of response for therapy.

Applicant maintains that to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without *undue* experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir., 1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 471 F.2d 1237, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. A patentee is not only entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. In re Anderson, at 1241 (citing Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 [1935]). Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 499, 502 (CCPA 1960). There is, therefore, no requirement for disclosure of every species within a genus. Applicant is entitled to claims that are commensurate in scope not only with what Applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicant has disclosed.

Applicant has provided an enabling disclosure for treatments including estrogen receptor modulators, estrogen receptor down-regulators, aromatase inhibitors, ovarian ablation, LHRH analogues and other centrally acting drugs influencing estrogen production. Accordingly, the claims

encompass determining responsiveness to a very wide range of drugs (antisense drugs, ribozymes, antibody therapy, organic and inorganic compounds).

In paragraph [0007], Applicants describe that the majority of breast cancers are dependent on the presence of estrogen and that many patients receive treatment to remove estrogen or to block the effects of estrogen on the tumor cells. To this end, many of these patients receive endocrine therapy. However, not every hormone positive tumor patient responds to endocrine therapy and therefore receives other types of therapy to either remove estrogen or to block its actions. Applicants then in paragraphs [0051] and [0143] list some of the possible therapies which may be used. One skilled in the art would recognize that while these treatments differ in structure and specific mechanism of action all in some way effect estrogen's effect on the tumor cells. The claims therefore encompass a subset of treatments with a common effect.

Applicant has also provided enabling disclosure for what the Examiner has term a broad genus of disorders, including benign and malignant disorders and specifically including ductal carcinoma in situ, lobular carcinoma, colloid carcinoma, tubular carcinoma, medullary carcinoma, metaplastic carcinoma, intraductal carcinoma in situ, lobular carcinoma in situ and papillary carcinoma in situ.

In paragraph [0007] Applicants describe that the majority of breast cancers are dependent on the presence of estrogen. There are several different types of sub-disorders which are described by the term breast cancer. One of the embodiments of the present invention is to differentiate breast cancer patients which may respond to a particular therapy or who may have a particularly aggressive form of breast cancer (See paragraph [0060]). As such, the term breast cancer encompasses the associated sub-disorders. Applicants have, in paragraphs [0061] and [0184], provided a list of such sub-disorders, thus enabling the invention.

Applicants have provided support to enable the use of any portion of the PITX2 gene for the determination of methylation status, but solely to advance prosecution claim 1 has been limited to the promoter region of the PITX2 gene. As described below, Applicants have provided working examples of such in Examples 1 and 2 of the present application as well as in several post filing publications as described in the declaration provided by Dr. Jurgen Distler.

Example 1 of the specification provides an outline of the data analyses methods (e.g., beginning at [0375]-[0401]; determination of disease-free survival ([0385]-[0388]; [0401]); analysis of methylation patterns for determination of therapeutic responsiveness (e.g., Tamoxifen) ([0389]-[0394] (Figures 41; 52-54 (see [0314]; Figures 61-62 [0321]-[0322]; Figures 71-71 [0331]-[0332]) and likelihood of distant relapse/metastases ([[0051]-[0066]; Figures 35-46). In order to advance prosecution, Applicants have amended claim 1 to more particularly define "characterizing" as including the prognosis of said subject disease free survival or likelihood of metastases of said subject; and/or probability of response of said subject to one or more treatment regimens. Applicants submit that Example 1, the figures identified above, and the specification as filed provide enablement for the use of the PITX2 gene methylation status for determining prognosis, distant relapse (metastases) vs. metastases free survival; and/or disease-free survival and/or probability of response to a treatment regimen (e.g., Tamoxifen), in contrast to the Examiner's assertions that no working examples are provided for PITX2.

Further, Applicants point to Example 2 of the application, beginning at [0402], where PITX2 (SEQ ID NO:23) in addition to other genes were validated as being effective markers for characterizing breast cancer. Paragraphs [0471]-[0480] provide data on two clinical endpoints used: disease-free survival and metastasis-free survival. Figures 61, 62, 103, 71, 72, 73 and 74 in particular provide clear data regarding the results of the assays showing that PITX2 is a marker capable of providing characterization of breast cancer as described above.

In addition, post-filing evidence further supports Applicants data and enabling disclosure. The Distler declaration describes data in Exhibit A which shows that PITX2 DNA methylation was used as a marker for outcome prediction in Tamoxifen-treated, node-negative breast cancer patients. The tests allowed a prediction of low-risk patients for example, who may be treated by Tamoxifen alone.

The Distler declaration also discusses data from Exhibit B which shows that DNA methylation of PITX2 predicts the risk of distant disease recurrence (metastases) in breast cancer patients.

The Distler declaration further discusses data from Exhibit C which provides support that that PITX2 DNA methylation is an independent predictor of poor prognosis and may be a marker for aggressive breast tumors.

The Distler declaration also discusses data from Exhibit D which shows that that PITX2 DNA methylation is a marker for disease recurrence and progression in node negative, steroid hormone receptor-positive breast cancer patients.

The Distler declaration further discusses the data from Exhibit E which shows that PITX2 DNA methylation in samples of blood and bone marrow plasma of breast cancer patients correlated with overall survival and distant disease free survival.

The Distler declaration additionally discusses the data from Exhibit F which provides evidence showing PITX2 DNA methylation is a marker for assessment of prognosis or prediction of a therapeutic response in patients with breast cancer. The marker was also used to show outcome predictions in breast cancer patients treated with Tamoxifen therapy as well as a biomarker to direct clinical decisions regarding therapy and used as a biomarker for aggressive breast tumors.

With respect to predictability, the Examiner cites several publications which didn't show a correlation between PITX2 methylation and response to therapy and its use as a prognostic marker. Applicants submit that the data provided in Examples 1 and 2 of the present application and the post filing evidence provided in the Distler declaration, both discussed above, provide more than adequate support for the use of PITX2 methylation as a prognostic indicator for determining which patients will respond to therapy as well as disease free survival.

Applicants submit that the claims as amended are fully enabled by the specification as filed and further supported by numerous post-filing references. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112.

CONCLUSION

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge the total amount of $650.00 to Deposit Account No. 07-1896 to cover the $245.00 fee for a Two Month Extension of Time and the $405.00 fee to cover a Request for Continued Examination. No additional fee is believed to be due in connection with this submission. However, the Commissioner is authorized to charge any fees deemed necessary with the filing of this paper, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number.

Respectfully submitted,

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Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer Number 28213